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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,460	10/16/2001	Daniel S. Kohane	0492611-0418 (MIT 9023)	5906

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Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109

EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	8

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,460	KOHANE ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-78* is/are pending in the application.

4a) Of the above claim(s) *25,28,34-36,41-44 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24,26,27,29-33,37-40,45-70 and 72-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election without traverse of the species of DPPC as the lipid having both positive charges on the choline portion and negative charges on the phosphatidyl portion (claim 27), albumin as the protein (claim 32), lactose as the sugar (claim 38), less than 10 micrometers as the diameter of the microparticles (claim 59); and embryonic stem cells as the cells (claim 72). Note that lipids comprising phospholipid and/or a choline portion embrace the elected species, and thus, will be searched and examined therein. In addition, the species of cellulose as a sugar has been rejoined for prior art search and examination.

Claims 25, 28, 34-36, 41-44, 71, directed to non-elected species, have been withdrawn by the examiner.

Claims 1-24, 26, 27, 29-33, 37-40, 45-70, 72-78, to which the following grounds are applicable, are pending.

The drawings are objected because the drawings are not formal and too dark for scanning.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for

patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-24, 26, 29, 30-33, 37, 39-40, 45, 46, 47, 49-62, 65-70, 73-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Grinstaff *et al.* (US 5,639,473), or under 35 USC 103 as being unpatentable over Grinstaff *et al.* (US 5,639,473).

The main thrust of the claimed invention is the making of a matrix or microparticle

composed of at least two components selected from a lipid (DPPC, any protein (albumin) and a sugar (cellulose or lactose). The microparticles can also be formulated so as to incorporate a stabilizer such as PEG or a synthetic polymer. The size of the microparticle can be less than 50 um (less than 10 um). The microparticles are employed for delivery of any known DNA of choice such as RNA, plasmid coding a protein of interest, *e.g.,* immunogen, viral antigen, protein of choice.

Grinstaff teaches the making of a matrix or microparticle composed of at least two components selected from a lipid (lipids composed of a choline and a phospholipid), any protein (albumin) and a sugar (cellulose), *e.g.,* see column 7 bridging column 8, column 8, lines 54-65 (albumin), column 9, lines 11-20, (synthetic polymer such as PEG or polyacrylic acid), column 12, lines 12-31 (phosphatidyl choline (PC) and/or proteins and/or poysaccharides such as cellulose. Polymeric shells as carriers for polynucleotide constructs, DNA or RNA are disclosed in Example 13. The size of the microparticle can be less than 50 um (less than 10 um, see example 46). Routes of administration are disclosed on column 26, second full par. The microparticles are employed for delivery of any known DNA of choice such as RNA, plasmid coding a protein of interest, *e.g.,* immunogen, viral antigen, protein of choice. The Grinstaff reference as a whole particularly teaches that any combination of biocompatible materials such as sugar, lipid and/or protein and/or PEG can be crosslinked to make a biocompatible polymeric shell, wherein the shell or its surface can be modified to incorporate any known emulsifier, surfactant and/or stabilizer. The polymeric shell would then be suitable to encapsulate any drug of choice such as DNA, RNA or plasmid

coding for a protein or antigen of interest. As such, it would also have been obvious for one of ordinary skill in the art of polymer or microparticle to employ any combination of ratio or percent weight of each of the biocompatible material as a matter of design choice for the making of the polymeric shell, particularly since the reference clearly teaches that as long as ultrasonic radiation and crosslinkers are employed, combinations of albumin, sugar, lipids and/or PEG can be formulated to make a polymeric shell designed for use as a carrier of any biologically active molecules such as known antigen coding plasmids.

Thus, Grinstaff anticipates, or in the alternative, renders the claimed invention as a whole *prima facie* obvious.

Claims 1-24, 26, 27, 29-33, 37-40, 45-69, 73-78 are rejected under 35 USC 102(e) or 102(a) as being anticipated by Edwards (US 5,985,309), or in the alternative, under 35 USC 103(a) as being unpatentable over Edwards (US 5,985,309).

Edwards teaches a polymeric microparticle of less than 10 um in diameter for use as a controlled release- encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein exipients (albumin) and a sugar (lactose), *e.g.,* entire disclosure, especially column 3 bridging column 4, column 4 bridging column 5, entire column 6, column 6 bridging column 7, column 7, lines 4-68, column 8, lines 7-19, column 11 through column 12. More specifically, Edwards teaches that any combination of biocompatible materials

such as biologically active agents, polymers, lipid surfactants and protein/sugar excipients can be used to make the encapsulated particles so that the particles are basically formulated to become a hydrophilic or hydrophobic complex of a positively or negatively charged therapeutic agents, wherein a surfactant and known protein/sugar excipients can be incorporated on or within the particle surface so as to enhance the biocompatibility and controlled release activity of the particles. Edwards also teaches on column 9 that the polymeric particles are preferably prepared by spray drying, and that the size of the particles can be between 5 and 30 um in diameter. Polymer and/or co-polymers concentrations can be used, for example, between 0.05 and 1.0 g/ml. Example 14 discloses the making of a formulation comprising particles (mean diameter 10 um) with 60% DPPC, 18% albumin, and 18% lactose. Furthermore, Edwards teaches (column 27) that depending on a preference of particularly desired aerodynamic properties of inhaled microparticles, the syray drying parametes such as concentrations of the surfactans, polymers and exipients can be adjusted accordingly by a person of ordinary skill in the art.

To the extent that Edwards do not teach explicitly minor modifications such as known DNAs, RNA or plasmids encoding for an antigen, ratios of agents being used in the formulations, and/or a particular combination of known matrix polymers, lipids and excipient(s), such would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a mater of design choice by a person of an ordinary skill in the art of polymer.

Thus, Edwards anticipates, or in the alternative, renders the claimed invention as

a whole *prima facie* obvious.

Claims 1-24, 26, 27, 29-33, 37-40, 45-70, 72-78 are rejected under 35 USC 103 as being unpatentable over Grinstaff taken with Wheeler (US 5,976,567).

The rejection of the base claims are applied here as indicated above in the 102 rejections.

To the extent that Grinstaff does not teach that the lipid surfactant can be DPPC, and that the carriers or particles can be used to transducer hematopoietic stem cells or embryonic stem cells *in vitro* and/or *in vivo,* Wheeler teaches that DPPC-based carriers (column 8, line 60) can be used to enhance the transfection and delivery of lipid/nucleic acids complexes into hematopoietic stem cells or embryonic stem cells *in vitro* and/or *in vivo* (column 28, lines 34-47).

It would have been obvious for one of ordinary skill in the art to employ any choline-based phospholipids such as DPPC in the lipid coated polymeric shell of Grinstaff. One of ordinary skill in the art would have been motivated to do so because Grinstaff teaches that any choline based phospholipids can be incorporated in the polymeric shell based carrier and that DPPC, as evidenced by Wheeler, is commonly used in the prior art as non-cationic lipids so as to adjust the hydrophobic properties and/or lipid bilayer forming properties in the making of a DNA delivery based lipid carrier.

It would also have been obvious for one of ordinary skill in the art to employ the polymeric shell of Grinstaff to delivery and/or transducer embryonic stem cells *in vitro* or

in vivo. One of ordinary skill in the art would have been motivated to do so because it is well-established in the prior art, as exemplified by Wheeler, that lipid nucleic acid particles can be used to enhance the DNA delivery and transfection into embryonic stem cells *in vitro* and/or *in vivo*.

Thus, the claimed invention, as a whole, was *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER